Effects of operation on blood coagulation

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EFFECTS OF OPERATION
ON
BLOOD COAGULATION

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Patients may clot to death as well as bleed to death following an operation. This clotting occurs because of an increase in the coagulability of the blood after such a procedure. In the severe stress of operations there is an increase in levels of fatty acids in the plasma. These fatty acids exist in the plasma as soaps. The soaps have coagulant effects that may be hazardous, especially in patients with clot times already low, as in atherosclerotics.

This thesis reports a study of postoperative hypercoagulability and other alterations that may influence the operative and postoperative courses of patients. In addition it reports the results of efforts to determine if the increase in fatty acids after operation could be prevented or reduced by the intravenous administration of calories at the time of operation and during the immediate postoperative period. If so, perhaps we could minimize the danger of postoperative thromboembolism.

The results did indeed document this postoperative hypercoagulable state as well as the protective effects of supportive carbohydrate administration. Of the patients tested, 93 per cent (25 out of 27) showed a decrease in coagulation times immediately following the stress of an operation. This
was a significant 40 per cent (4.5 minutes) average decrease in the coagulation time.

However, only 60 per cent (15 out of 26) of the patients tested showed an increase in fatty acid levels immediately following such a procedure. The comparative percentage difference between fatty acid elevations and coagulation times can be explained on the basis of carbohydrate administration. Eighty five per cent (11 out of 13) of those patients who received supportive calories (100 grams of dextrose intravenously over a four-hour period) showed striking reductions in their fatty acid levels. Conversely, 85 per cent (11 out of 13) of those patients who did not receive this caloric support showed elevations in their fatty acid levels.

Other significant results include a rather remarkable immediate postoperative decrease in fibrinogen levels in 88.5 per cent (26 out of 26) of the patients tested.

Thus there is a definite relationship between stress, fatty acids and coagulation times in the postoperative patient. Certainly there are a sundry of factors responsible for the postoperative hypercoagulable state. We have demonstrated one very important factor, elevated fatty acids in plasma. In addition we have shown how to minimize the actual fatty acid mobilization during stress and still meet the energy require-
ments of a stressful situation.

***** METHODS AND MATERIALS *****

A. PATIENTS

Thirty-four surgical patients were chosen at random, regardless of past history or operation to be performed. Fifteen females and 18 males comprised the group. Body builds ranged from slender to obese. Histories obtained included the following: cancer (8 patients), cardiac (8), atherosclerotics (4), diabetes (3), hypertension (2), stroke (1), Parkinsonism (1), Laennec's cirrhosis (1), Charcot-Marie-Tooth syndrome (1), and idiopathic thrombocytopenic purpura (1). Operative times varied between 18 and 245 minutes. The average time of operation was 96 minutes.

B. INTRAVENOUS FLUIDS ADMINISTERED

The patients were divided into two groups. Those patients whose hospital numbers ended with an odd figure were designated as Group A and were essentially the control group. These patients were given two liters of an electrolyte solution, WITHOUT dextrose, over a four-hour period beginning with sample number two, or the immediate preoperative sample.
Group B consisted of those patients whose hospital numbers ended with an even figure. These patients were given two liters of an electrolyte solution containing 5 per cent dextrose, again over a four-hour period beginning with the preoperative sample.

C. SAMPLE TIMES

Five blood samples were taken from each patient. The sampling schedule was as follows:

(1) Sample number ONE was taken before supper the evening before operation. This sample was used as a base line essentially representing a fasting level.

(2) Sample number TWO was taken in the operating room immediately prior to the operation. Intravenous fluids were started at this time. This sample represented the levels attained as a result of psychologic stress as the patient approached his or her operation and the effects of preoperative medication.

(3) Sample number THREE was taken in the recovery room immediately after the operation. This sample represented the immediate response to the operative stress.

(4) Sample number FOUR was taken four hours after the operation. The intravenous fluids, administered
over a four-hour period, had been completed except for a few exceptions. This sample reflected the patient's ability to return to preoperative levels.

(5) Sample number FIVE was taken before breakfast the day after the operation. This sample again reflected the patient's ability to return to preoperative levels and did indeed represent true fasting levels.

D. TECHNIQUES EMPLOYED

1. Collection of blood samples: The usual antecubital venipuncture was employed using a 20 gauge needle and a 20 milliliter syringe. Each sample consisted of 24 ml. of blood. Two ml. of blood were placed into each of two saline rinsed Lee-White tubes. Nine ml. were placed into standard sized test tubes and allowed to clot. The serum from these tubes was used for the fatty acid, total lipid and lipase determinations. Nine ml. were placed into a standard tube containing 1 ml. of oxalate anticoagulant. This plasma was used for recalcified clot times and fibrinogen determinations. The latter two samples were immediately refrigerated until the following procedures could be performed.

2. Coagulation times: These were determined by a modified
Lee-White technique. Timing was begun at the time of venipuncture. Two ml. samples were immediately placed into each of two saline rinsed Lee-White tubes. The first tube was tipped every 30 seconds until a completely firm gel was formed as evidenced by inversion of the tube. The second tube was likewise inverted every thirty seconds until a FIRM gel was formed. This was the end point.

3. Ionic Fatty Acid Determinations (1)

   a. The serum was separated from the samples and centrifuged to separate the erythrocytes completely.

   b. Two milliliters of serum was placed in a 25 ml. test tube, using a teflon stopper.

   c. Ten milliliters of extraction mixture (39 ml. isopropanol, 10 ml. heptane and 1 ml. 1N sulfuric acid) and 4 ml. of distilled water were added to the serum. The tube was shaken for five minutes and then stood to separate phases.

   d. Five milliliters of the heptane phase was pipetted into a 15 ml. centrifuge tube.

   e. Five milliliters of dilute sulfuric acid was added to the centrifuge tube, the mixture was shaken for 5 minutes and then centrifuged for 5 minutes.

   f. Three milliliters of the supernatant washed
heptane phase were placed into a suitable test tube.

  g. Two drops of 0.1 per cent thymolphthalein in isopropanol (colorless at 9.3 - 10.5 blue) were added and stirred by washed nitrogen (alkali-ethanol). This was titrated to a faint blue with 0.02N potassium hydroxide in isopropanol employing the Gilmont ultramicroburet. This end point persisted for 5 seconds. Blank procedures and titrations were run.

  h. Ionic fatty acid values were calculated from net alkali used on the final 3 ml. extract.

4. Fibrinogen Determinations (2):

  a. Two tubes containing 9 ml. of saline and 1 ml. of plasma were mixed thoroughly.

  b. Two tubes containing 9 ml. of Fowell mixture (ammonium sulfate 13.3 per cent and sodium chloride 0.9 per cent and 1 ml. of plasma were likewise mixed thoroughly.

  c. The spectrophotometer (Spectronic 20) was set at 510 millimicrons.

  d. The optical density of the plasma-saline mixture was read and recorded as compared to distilled water zero. This recorded the turbidity and/or hemolysis. The same cuvette was used for the plasma-saline and plasma-Fowell mixture.
e. With the plasma-saline, the instrument was reset to an optical density of zero. The plasma-saline was poured out, the curvette rinsed, and filled with plasma-Fowell mixture.

f. Three minutes after mixing, the optical density of the plasma-Fowell mixture was read and compared to the plasma-saline zero. This reading was recorded and represented the milligrams of fibrinogen in 100 milliliters of plasma.

5. Lipase Determinations (3):

a. Three milliliters of Sigma emulsion (olive-acacia) were mixed with 1 ml. of Tris buffer and 2 ml. of 0.9 per cent saline. This was used as the control.

b. Likewise 3 ml. of Sigma emulsion were mixed with 1 ml. of Tris buffer and 1 ml. of 0.9 per cent saline. This was the test solution.

c. Both tubes were incubated for 5 hours.

d. Following incubation, 1 ml. of the patient's serum was added to the test solution.

e. Using a glass electrode, the contents of both tubes were titrated to a pH of 8.

f. The difference in sodium hydroxide requirements
between the 2 tubes was a direct measurement of the milliequivalents of fatty acids produced by 1 ml. of serum. This resulted in a direct measurement of lipase activity.

6. Total Lipid Determinations (4):

    a. Five-tenths of a milliliter of serum was added dropwise to 9.5 ml. of Bloor's mixture (1 volume of ethyl ether plus 3 volumes 95 per cent ethyl alcohol) in a 10 ml. graduated tube.

    b. The mixture was placed in a water bath at 60 degrees centigrade for 30 minutes.

    c. The mixture was then cooled to room temperature. Bloor's mixture was added to restore the 10 ml. total volume, mixed and the liquid phase was separated by filtration (filter paper in small funnels) or by centrifugation.

    d. One milliliter of the filtrate was pipetted into another tube, and the solvent evaporated to dryness in a boiling water bath.

    e. One and one-half milliliters of p-Dioxane was added, placed in boiling water for 1 minute to dissolve the lipids, and then cooled to room temperature.
f. Five milliliters of dilute sulfuric acid solution (40 ml. of concentrated sulfuric acid plus distilled water to make one liter) was added and produced a spontaneous emulsion of lipids.
g. The mixture was allowed to stand at room temperature for 60 minutes.
h. The optical density was then read at 650 millimicrons using a Bausch and Lomb Spectronic 20.
i. A blank and triolein standard were run at the same time.
j. Finally \[ \frac{\text{Net optical density of sample}}{\text{Net optical density of 1 per cent triolein}} \]
equals the per cent of lipids.

7. Recalcified Clot Times (5):

a. Two-tenths of a milliliter of 0.1N calcium chloride was added to 1.8 ml. of saline.
b. Likewise 0.5 ml. of 0.1N calcium chloride was added to 1.5 ml. of saline.
c. Two milliliters of plasma were placed into a separate tube.
d. All 3 tubes were then incubated separately in a water bath at 37.5 degrees centigrade.
e. One milliliter of the oxalated plasma was
then added to each of the 2 tubes containing the calcium chloride.

f. The tubes were then tilted at 15 second intervals, with minimal agitation, until the plasma clots. This is the end point.

***** RESULTS *****

A. LEE-WHITE COAGULATION TIMES

As noted in Figure 1, the fasting Lee-White coagulation times of the 27 patients tested were essentially within the 9 to 13 minute range with a mean of 11.5 minutes. This compares favorably with comparable procedures of determination although in the upper range of normal.

The preoperative (psychological) stress resulted in a decrease in clot time to a mean of 10.1 minutes. This drop was not particularly important in most of the patients tested, although in two very anxious patients, the drop was quite significant.

The major drop in clot times came immediately after the actual stress of operation. This decrease, an average of 4.5 minutes per patient, was particularly significant in ten patients whose clot times decreased to a dangerous 2.5 to 5.5 range.

Although 93 percent (25 out of 27) of the patients
tested showed a decrease in clot times immediately after
the operation, there was a significant difference between
those patients who received supportive caloric therapy
and those who did not. Those with dextrose had an imme-
diate postoperative mean clotting time of 7.77 minutes,
whereas those who had not received dextrose had a mean
clotting time of 6.29, a difference of 1.48 minutes.
Within 4 hours the clotting times of those who had
received dextrose quickly returned to normal mean of 9.96
minutes, whereas the clotting time of those who had not
received dextrose remained low, 7.43 minutes on the average.

B. IONIC FATTY ACIDS

Figure 2 shows the effects of stress, psychological
as well as operative, on fatty acid mobilization. The
mean fasting level of 0.885 mEq/L was certainly on the
high side of normality.

The psychological stress of operation definitely
resulted in an increase in the IFA levels. The levels
reached a preoperative mean of 1.18 mEq/L. Eighty-one
per cent of the patients showed this fatty acid mobiliza-
tion resulting from the preoperative psychological stress
associated with an operation.

After the trauma of operation, the mean levels
remained high, although decreasing slightly to 1.07 mEq/L. However, this figure is quite misleading as there was a great disparity between the IFA levels of those patients who had received dextrose and those who had not. Indeed, the IFA levels of 85 per cent (11 out of 13) of the patients tested who had received dextrose were lowered significantly to a mean of 0.856 mEq/L. On the other hand, the immediate postoperative IFA levels of 85 per cent (11 out of 13) of the patients tested who had not received dextrose were elevated to a mean of 1.28 mEq/L. These high levels persisted for at least 4 hours after operation, gradually decreased, but remained elevated the day after operation.

This fatty acid mobilization as a result of stress was especially noticeable in the 10 patients previously mentioned with clot times after operation in the dangerous 2.5 to 5.5 minute range. These patients ALL had immediate postoperative IFA levels well above the mean.

C. FIBRINOGEN LEVELS

As noted in Figure 3, the mean fasting fibrinogen level of the patients tested was 247 mg per cent, slightly on the high side of normal. With psychological stress apparently having no effect, these levels fell sharply immediately after the operation. The postoperative
mean was found at a low level of 175 mg. per cent. There was no significant difference between those patients who had received dextrose and those who had not.

The fibrinogen was quickly replaced as the 4 hour postoperative mean level was 219 mg. per cent. On the other hand, the 24 hour postoperative fibrinogen level was found at 306 mg. per cent, definitely ELEVATED above the range of normality.

D. LIPASE ACTIVITY

Little information was gained from the lipase studies. The findings were scattered, varying widely, with no definite trend associated with the stress of operation. The mean fasting lipase levels was found to be 26 units per cc. This decreased to 21 units/cc immediately before the operation, remained at this level after the operation, decreased to 18 units/cc 4 hours afterwards and then increased to the fasting level of 26 units/cc 24 hours after the operation.

The only consistent finding was one of an inverse relationship between the IFA levels and the lipase activity. Comparing Figures 2 and 4, one can see that when IFA levels were at their highest, the lipase levels were at their lowest, and vice versa.

E. TOTAL LIPID LEVELS

As noted in Figure 5, the total lipid levels were
quite constant throughout the preoperative and postoperative periods. A quite normal mean fasting value of 0.77 per cent was found. This decreased to 0.71 per cent preoperatively, remained at this level immediately after the operation, fell to 0.65 per cent four hours after the operation, and then returned to a mean level of 0.69 per cent 24 hours later. All of these values were within the normal range. There was no significant difference between those patients who had received carbohydrates and those who had not.

F. RECALCIFIED CLOT TIMES

The recalcified clot times were performed with no statistical correlation. Several values were grossly in error and thus had to be disregarded. The procedure is a modification of the standard recalcified clot time test and is as yet in the developmental stage.

G. PROCEDURE TIME-CLOT TIME

Figures 8 and 9 were attempts to correlate procedure time to postoperative hypercoagulability of the blood. No definite trend line could be developed with any significance.
acids are apparently bound to lipoprotein. "Free fatty acids" was finally adopted in full knowledge of the fact that they are not "free" in the sense of being non-protein bound (although a very small percentage is, depending on the dissociation constants of the complexes formed by the individual acids and proteins), but they are free in the sense of "not bound by covalent linkages" (7). The term "ionic fatty acids" (IFA) has come into vogue recently since it is believed that these substances exist as ions at physiologic pH values. Hence, throughout this paper, the term IFA is used with full reference to the preceding descriptions.

c. IFA Source and Transport

These ionic fatty acids in plasma may originate from three principal sources: from alimentary sources, from intravascular lipolysis of plasma, and from fat depots (8). The first possibility is self explanatory, depending upon dietary intake and absorption-transport abilities. The second possible source, intravascular lipolysis, may occur under normal conditions, but the amount of IFA delivered to plasma by this route appears to be of minor importance
as a source of the total circulating IFA. Hence the third source, mobilization of IFA from the fat depots, appears to be primary in importance.

The observation that IFA are extracted from plasma by heart muscle (9) and by working leg muscle, together with the rapid output of \( C_{14}O_2 \) after intra-venously injected labelled IFA (10) indicates the importance of IFA in plasma as a transport form for fat for metabolic demands. According to some authors, however, all IFA removed from plasma seems not to be directly oxidized (11).

The levels of IFA in plasma appears to be influenced by countless numbers of factors. These will be discussed in the subsequent pages.

d. **Thrombus Formation Accelerated by IFA**

Certainly lipids have long been known to exert important effects upon blood coagulation. The crude cephalin of Howell accelerated clotting (12) whereas the extraction of lipid from plasma by Macfarlane, Trevan and Attwood inhibited its coagulation (13). Many studies have stressed the role of phospholipids in coagulation. Indeed, thromboplastin generation will not occur without optimal concentrations of phospholipid.
Several investigators have shown that the addition of fatty acids to citrated plasma shorten the clotting time (14, 15, 51, 52). The concentrations of fatty acids used were within the range of the levels of circulating IFA in man. Chandler devised a technique for making artificial thrombi in a rotating circular plastic tube (16). These thrombi had a white head of platelets and leukocytes and a long fibrin tail containing trapped red blood cells. They were similar in microscopic appearance to the thrombi occurring in disease. Connor and Poole have found that the thrombus-formation time of rat blood was shortened greatly by the addition of long chain, saturated fatty acids but was unaffected by either short chain, saturated fatty acids or by long chain, unsaturated fatty acids (17).

2. Stress-Hormone-IFA Interrelationships
   a. Lipid Mobilizing Hormone

Seifter and Baeder in 1954, discovered a lipid mobilizing hormone in the plasma of man and animals. They succeeded in isolating the hormone from the posterior pituitary glands of hogs (18). They demonstrated that this hormone is increased by cortisone, stress and starvation (19). When it is given to fasting subjects there is an increase in cholesterol and IFA
in the plasma. If sustained levels of the hormone are given to patients on a low fat diet, a sustained hyperlipemia is induced, but with non-fasting patients, or patients on a high fat diet, no such response is demonstrable (20). Seifter and Baeder further showed that the administration of the lipid mobilizing hormone results in the mobilization of triglycerides from the mesenteric depots, but this was not necessarily reflected in the peripheral blood. It is postulated that this depends upon the ability of the liver to utilize fat. With adequate glycogen stores, the liver can utilize fat whereas with glycogen depletion it cannot (19).

b. Role of the sympathetic nervous system

Two distinct lipid mobilizing activities of epinephrine and norepinephrine should be recognized. First, they stimulate the release of ionic fatty acids from tissue depots; second, they cause an elevation of serum lipoprotein levels (21). The rise in IFA after epinephrine is marked but short lived. It appears promptly but it cannot be sustained either by continuous infusion of large amounts of epinephrine in saline solutions or by the
administration of long acting epinephrine in oil. The IFA level returns to normal before significant elevations in the cholesterol and phospholipid values are noticed.

Havel and Goldfien have recently been quite successful in demonstrating the importance of the sympathetic nervous system hormones on IFA plasma levels (22). They observed an increase in oxygen consumption associated with an increase in plasma IFA concentration in anesthetized dogs under total epidural sympathetic blockade. The possible importance of the effect of norepinephrine on plasma IFA is suggested by the profound decrease in the rate at which IFA is added to plasma after administration of hexamethonium. This change, presumably reflecting decreased mobilization of adipose tissue triglycerides, is probably the result of decreased liberation of norepinephrine from sympathetic nerve endings in the parenchyma of adipose tissue. Blockade of adrenal medullary secretion cannot be the decisive alteration, since the response to hexamethonium is similar to intact and adrenalectomized dogs.

The rise in plasma IFA accompanying anxiety or discomfort in humans and decreasing depth of anesthesia
in dogs provides further evidence of the role of the sympathetic nervous system in the mobilization of fatty acids from adipose tissue (53, 54, 55, 56). Pentobarbital anesthesia in dogs is accompanied by diminished adrenal secretion of norepinephrine and epinephrine. Decreases in the depth of anesthesia are associated with increases in medullary secretion. This effect of anesthesia may apply to the extra-adrenal sympathetic nervous system as well, since lessening of anesthesia in an adrenalectomized dog is accompanied by a rise in plasma IFA concentration. Furthermore, alterations in depth of anesthesia did not result in changes in plasma IFA concentrations in dogs given hexamethonium. The physiologic significance of the effect of the sympathetic nervous activity on the mobilization of fatty acids from adipose tissue is thus quite great in the stressful situation. This mechanism can and does provide for rapid mobilization of fatty acids for energy needs of peripheral tissues. The reduction in plasma IFA levels in fasting dogs produced by hexamethonium suggests that the tonic activity of the sympathetic nervous system may provide for continuous release of IFA at a level that can be modified by insulin and other humoral agents.
c. Anterior Pituitary-Adrenal Response to Stress

The stress response of the adrenal cortex is of prime importance to the surgeon. Stress results in the immediate release of pituitary adrenocorticotropic hormone (ACTH) (23, 59). Neurosecretory centers in the ventral hypothalamus control the release of anterior pituitary ACTH following an operative injury (24). Nerve impulses from the injured area are essential for initiating this response. Trauma influences these hypothalamic centers through various neural and possible humoral mediators. By neural connections, the posterior pituitary is influenced to discharge antidiuretic hormone and by probable humoral mediators via the hypophyseal portal circulation the anterior pituitary discharges thyroid stimulating hormone and ACTH.

Increased adrenal cortical activity postoperatively has been shown by various methods, including the measure of blood and urine steroids, eosinophil counts, and the determinations of serum, urine and sweat electrolytes.

The physiologic action of ACTH and cortisone as particularly related to operation is quite extensive according to Cole and others (15). There is a retention
of sodium chloride and water, but a loss of potassium, nitrogen, phosphorus and calcium. The peripheral tissues utilized more fat and spare carbohydrate, with a resultant transitory rise in ketone bodies. Amino acids are diverted toward deamination with production of carbohydrates (gluconeogenesis), resulting in a negative nitrogen balance. The normal blood count is rarely affected, but in many disease states there is a reticulocytosis and platelets are increased. A neutrophilia is produced along with an eosinopenia and an initial decrease in lymphocytes, followed by a compensatory rise. There is a fall in serum gamma globulin. Coagulation time is decreased and the heparin titer increased.

The effect of the anterior pituitary on fat mobilization is well established (26, 57, 58). The hypophysectomized animal is in positive fat balance and has a higher proportion of body fat than normal animals on the same caloric intake. The effects of treatment with anterior pituitary extract or purified growth hormone on fat metabolism are essentially the reverse of those following hypophysectomy. The total fat content of the body decreases concomitantly with a net increase in protein. Fat is rapidly mobilized to the
liver producing a fatty liver and ketosis (27, 28). Farber's work is suggestive that an adrenal cortical hormone is necessary for the fat-mobilizing effect of the anterior pituitary extract, but is not responsible for it (29).

Under nonstressful conditions, the pituitary-adrenocortical system appears to be regulated, at least in part, by a negative feedback mechanism whereby an increase in plasma cortisol suppresses corticotropin (ACTH) secretion while a decrease in plasma cortisol leads to an increase in the secretion of ACTH. In response to certain stresses, however, both ACTH and cortisol are secreted in increased quantities. Estep et al attempted to determine the role, if any, which the negative feedback mechanism plays in regulating ACTH secretion during the acute stress of pelvic laparotomy (30). As compared with preoperative levels, they found that plasma 17-hydroxycorticoids increased by 17-36 ug/100 milliliters and urinary 17-hydroxycorticoids increased by 4-20 mg/day in 22 patients undergoing pelvic laparotomy without exogenous steroids. Similar increases in 17-hydroxycorticoids were observed in 10 patients given exogenous steroids before and during the operation. Thus it is realized that during
the stress of operation, the behavior of the human pituitary-adrenal system does not conform to the specifications of a negative feedback mechanism, thus allowing for higher adrenal hormonal levels.

d. Insulin and IFA

It is noted that with the injection of insulin there is a rapid decrease in IFA levels. This alteration occurs with, or even preceding the fall in blood glucose. Later, when glucose levels return to normal, the IFA levels follow in close parallel. It is of interest to note that diabetic patients with abnormal glucose tolerance curves show corresponding abnormalities of IFA responses (31).

Gordon demonstrated that an injection of insulin or glucose abolishes the usual arteriovenous increment of IFA concentrations in blood from adipose tissue (32). The administration of glucose or insulin to rats diminishes the breakdown of triglycerides and reduces the oxidation of labelled fatty acids (33, 34). The amount of fat in adipose tissue is increased by insulin presumably because of increased lipogenesis and reduced output of fatty acids (35, 36). It has been shown by several workers that insulin decreases the release of fatty acids from tissue stores, but does not accelerate
Their removal from the blood.

The findings of Bierman, Roberts and Dole support the theory that tolbutamide stimulates insulin discharge but does not in itself promote oxidation of glucose (37). As noted before, IFA levels rise when carbohydrate utilization is reduced, and fall when carbohydrate oxidation is enhanced. This relationship reflects actual utilization of glucose rather than the mere availability of the sugar, because glucose is ineffective in lowering the IFA levels under conditions of insulin deficiency. With diabetic ketosis and with fasting, IFA levels rise progressively. The administration of insulin causes a drop in IFA in either case, whereas glucose administration apparently brings about this effect only in fasting subjects. It seems likely therefore, that tolbutamide is effective in relieving ketosis only when the pancreas is capable of responding with an increased output of insulin. Diabetics responding to tolbutamide with a prolonged depression of blood sugar show a comparable sustained reduction of IFA concentrations.

e. Stress and Thyroid Activity

The influence of surgical stress on thyroid
function has been the subject of many studies. Contradictory results have been reported in animals and humans, depending on differences in experimental conditions. Most of the early investigators noted that severe surgical stress decreased thyroid radioiodide accumulation and hormone release from the gland in euthyroid patients (60). Similar effects have noted after the administration of ACTH and cortisone and it has been assumed that the depression of thyroid function after surgical stress mainly depends on the increase of these hormones (38). On the other hand, thyroid hormones also influence the adrenal function. Exogenous thyroxine increases the excretion of cortical steroids and results in adrenal hyper trophy (39).

As opposed to earlier findings, Gejrot and Notter have just recently found an increase in the uptake of I-132 during the immediate postoperative period, followed by a period of reduced hormone release, which in severe operations may last as much as one week (40).

Little is actually known concerning the metabolic relationships between thyroid hormones and IFA levels. It has been proposed that since thyroid hormones directly regulate the basal metabolic rate, they no
doubt have a marked influence on IFA levels. As the
energy demand is increased, fatty acids are rapidly mobili-
zed to meet the increased energy requirements with
resultant higher normal levels. Much work needs to
be done in regard to this relationship.

3. Protective Effects of Carbohydrate Administration

It has been shown previously that the adminis-
tration of glucose either parenterally or orally will
reduce IFA levels and will return previously elevated
IFA levels to normal (1). The decrease in IFA is
even more marked than that observed following the
ingestion of a mixed meal. A 50 gram dose of glucose,
either orally or intravenously reduces the IFA to a
minimum of approximately 0.2 mEq/L. This minimum is
reached at about 1 1/2 hours after the administration
and slowly returns to initial values. Obese sub-
jects, with higher fasting concentrations of IFA,
show the greatest changes in concentration, but in
all cases the administration of glucose results in
some reduction in the level. Measurement of both
glucose concentration and IFA shows a closely correla-
ted reciprocal variation. Generally, it can be
stated that with an increase in glucose metabolism
there is a decreased output of fatty acids from tissue
stores.
Wadstrom and co-workers confirmed that the infusion of glucose after operation decreases the concentration of IFA in plasma (42). They noted that the effect was inversely related to the blood sugar level and this relationship persisted as long as the infusion continued, but was no longer demonstrable one hour after the administration was stopped. Their findings suggest that glucose administration postoperatively results in an actual reduction in the mobilization of fat from fat depots.

B. CAUSAL RELATIONS AS PROVEN BY THIS INVESTIGATION

1. Stress-Coagulation Times

There has been a sundry of research articles published on the subject of hypercoagulability of blood after stressful situations. Davis and Porter demonstrated that after the severe stress of burns and hemorrhagic episodes in dogs, the coagulability of the blood increases (43). Davis and Olney demonstrated the hypercoagulability of blood after the stress of child birth (44). One could cite other authors who have induced some stressful situation in man and animals and demonstrated the same hypercoagulable state.

The present study bears out this concept. Regardless of the extent of supportive carbohydrate administration, 93 per cent (25 out of 27) of the
patients tested showed a decrease in coagulation times immediately after the stress of an operation. This was a significant 40 per cent (4.5 minutes) average decrease in coagulation time per patient. As noted in Figure 1, the 27 patients had a mean preoperative time of 7.0 minutes and a 4 hour postoperative time of 8.6 minutes. Ten patients showed a dangerous immediate postoperative coagulation time in the 2.5-5.5 range. Also of interest is the fact that the 2 patients who failed to show such a decrease in coagulation times both underwent simple "closed" orthopedic procedures under general anesthesia. Thus, with statistical data such as this, it is not difficult to conclude that after a stressful situation such as an operation, the coagulation time of the blood is indeed decreased, in some instances to rather dangerous levels.

2. Stress-Coagulation Time-IFA Levels

The endocrine response to stress and the lipid mobilizing effect of these hormones have been discussed in the preceding pages. Several authors have postulated and partially proven that in response to a stressful situation, whether it be traumatic or psychologic, there is an increase in IFA mobilization and that these
soaps in plasma result or add to a hypercoagulable state. Thus our results have shown a direct correlation between stress, coagulation times and plasma IFA levels. As stated in the preceding paragraph, we found that 93 per cent of the patients tested showed a decrease in coagulation times (an average of 4.5 minutes per patient) immediately after the stress of an operation. However we found that only 60 per cent (15 out of 26) of the patients tested showed an increase in IFA levels immediately after the operative procedure. As shown in Figure 2, the mean levels rose from 0.885 mEq/L fasting to 1.02 mEq/L immediately after the operation. There was a great disparity between those patients receiving dextrose and those who did not. This will be discussed later. It is of interest that ALL 10 patients in the dangerous immediate postoperative coagulation time range of 2.5-5.5 minutes showed IFA levels well above the mean, varying from 0.97 to 1.97 mEq/L. This finding has led us to believe that it is these high levels of plasma IFA that are particularly dangerous in the postoperative patient.

3. Protective Effects of Carbohydrate Administration

Theoretically then, if we could reduce these high IFA levels postoperatively, we could, in turn, reduce
or minimize this thromboembolic potential. Indeed, Wadstrom and co-workers showed that infusion of calories in the form of intravenous glucose AFTER operation decreased the concentration of IFA in plasma for as long as the infusion was continued. The present investigation was directed towards the infusion of glucose at the ONSET of operation, thereby attempting to reduce the IFA mobilization DURING the operative stress as well as during the postoperative period. This we accomplished. As noted in Figure 2, those patients who received dextrose during operation showed no rise in IFA levels postoperatively. Instead, striking IFA reductions were noted in 85 per cent (11 out of 13) of these patients. These low IFA levels were maintained as long as the intravenous calories were administered.

Conversely, 85 per cent (11 out of 13) of those patients who did not receive supportive caloric therapy showed elevations in their fatty acid levels. These high levels persisted for at least 4 hours after operation, gradually decreased, but remained elevated the next day.

4. Operation and Fibrinogen Levels

As noted in Figure 3, the fibrinogen levels were
decreased rather sharply immediately after the operation. Certainly the hemostatic mechanisms are operating at peak levels during the traumatic operative procedure. Circulating fibrinogen is quickly used up in the necessary clotting processes. These fibrinogen levels were quickly restored to normal levels and indeed are within the range of normality 4 hours after operation. Apparently there is an "over correction" of this deficit as higher than normal levels were noted in nearly all of the 24 hour postoperative samples. Perhaps this is a significant factor in the postoperative hypercoagulable state?

5. IFA and Lipase Activity

A very surprise inverse relationship was demonstrated between the IFA levels and the lipase activity. Comparing the results in Figures 2 and 4, one can see that when the IFA levels were at their highest, the lipase levels were at their lowest, and vice versa. No explanation is offered as to these unexpected findings.

C. OTHER FACTORS INVOLVED IN POSTOPERATIVE HYPERCOAGULABILITY

In the preceding pages, I have outlined and partially explained several of the factors responsible for the postoperative and post-stress hypercoagulable state. There
remain, however, a sundry of other elements or factors which add to or subtract from this potentially lethal condition. It is not the purpose of this study to investigate all of them, but several of them do bear mentioning. Hardaway and co-workers have recently written several papers concerning what he calls disseminated intravascular coagulation (45, 46, 47, 48, 49). He very expertly discusses the clinical, pathologic and hematologic changes which he found in common. He also listed a number of factors which he feels important in the formation of thrombi. I feel these factors are worth mentioning in conjunction with our recent studies.

1. Coagulability of the Blood

This has been discussed in preceding pages.

2. Rate of Blood Flow

Probably stasis predisposes to coagulation.

This results from many circumstances, but the following are important in the operative patient.

a. Hypotension associated with a low cardiac output and peripheral arteriolar spasm.

b. Capillary dilatation. Under circumstances of tissue anoxia, poor capillary perfusion, or injury, there is a great increase in local activation of histamine in the tissues, probably secreted by mast cells.
or endothelial cells. This results in pre-capillary sphincter relaxation permitting all capillaries to fill.

c. **Arteriovenous shunts.** Related to the stagnation in dilated capillaries is stagnation in capillaries sidetracked by arteriovenous shunts during adrenal medullary stimulation. This blood in the bypassed capillaries is completely stagnant and especially susceptible to coagulation if the blood is hypercoagulable.

d. **Arteriolar spasm.** Many factors being involved, this spasm promotes formation of intracapillary clotting by decreasing capillary flow. Adrenal medullary hormones apparently cause both arteriolar spasm and hypercoagulability (47). Evidently clotting can promote arteriolar spasm and arteriolar spasm can promote clotting in a vicious cycle (48).

e. **Stasis due to pressure on veins.** A prime factor in thrombophlebitis of pregnancy, this type of stasis plays a great part in coagulation in large vessels.

3. **Coagulating Substances Introduced Into the Blood Stream**

a. **Thrombin injection.** This as evidenced in Hardaway's earlier experiments (49).

b. **The clotting factor in red cells released by hemolysis.**
This apparently must be assisted by other factors, such as adrenomedullary hormones, shock, and vasospasm to produce an effect.

c. **Bacterial endotoxins and exotoxins.** These may be artificially introduced or released in gram-negative septicemia with destruction of bacteria in the blood.

d. **Tissue thromboplastin,** as in crush or other injury.

e. **Carcinoma and tissue necrosis related to it.**

f. **Necrotic tissue** from any source.

g. **Particulate matter.** Apparently, amniotic fluid embolism produces its intravascular clotting by the presence of particles in it, as filtered amniotic fluid produces no detrimental results when injected, whereas unfiltered amniotic fluid does. Other particulate matter, such as starch, kaolin, etc., will do the same (50). These probably act by increasing surface activation.

h. **Trypsin or other proteolytic enzymes** either from the pancreas or artificially introduced. These may split fibrinogen, as does thrombin, producing fibrin.

i. **Certain snake venoms.**

j. **Premature separation of the placenta results in the introduction of substances, probably thromboplastins,** into the blood stream.
K. Peptone.

4. Injury to Blood Vessel Walls
   This causes immediate platelet accumulation and initiates thrombus formation.

5. Activation of Surface Clotting Factors
   These factors, the Hageman factor being the best known, are important in tubing, oxygenating equipment, etc., used in extracorporeal circulation.

6. Exogenous Drugs
   Certain correlations have been made over a period of time between the increased coagulability of the blood and the administration of various substances. Thus, with the administration of therapeutic doses of the following agents, a definite increase in the coagulability is noted: digitalis, penicillin, aureomycin, streptomycin, terramycin, mercurial diuretics, metallic antisyphilitic drugs, heavy metals, mustard gas, certain anesthetics, estrogens, ACTH, and probably many more (61, 62, 63, 64).

****** SUMMARY AND CONCLUSIONS******

Many more patients clot to death than bleed to death after an operation. This postoperative hypercoagulable state results from a sundry of clotting factors. A major factor may well be high levels of fatty acids in the plasma as a result of their
increased mobilization to meet the energy demand of a stressful situation. These fatty acids exist as soaps in plasma and have coagulant effects which may be of great significance in patients with low fasting or baseline clotting times.

This thesis reports a study of this postoperative hypercoagulability and other alterations that may influence the operative and postoperative courses of patients. Particular emphasis was placed on the stress-fatty acid-coagulation relationship and the protective effect of supportive carbohydrate therapy.

Thirty-three surgical patients were chosen at random and divided into two groups. One group received supportive caloric therapy during and after the procedure while the second group did not.

Both groups showed a marked postoperative decrease in clot times. Ten patients demonstrated a serious hypercoagulable state as their postoperative clot times dropped to a very low and dangerous range. All ten of these patients demonstrated marked elevations of their IFA levels. The IFA mobilization response to the stress of operation in the remaining patients was quite variable. Overall, only sixty per cent of the patients tested did show an increase in IFA levels immediately after the operation. A somewhat greater percentage demonstrated elevated IFA levels as a result of the preoperative or psychological stress.

The sparing effects of supportive carbohydrate administration
was clearly demonstrated. Nearly all (85 per cent) of the patients receiving dextrose during and after the operation showed a decrease in IFA levels. This IFA suppression continued for as long as the intravenous administration of dextrose was continued. Conversely, nearly all (85 per cent) of those patients who did not receive dextrose showed elevated IFA levels postoperatively. Their IFA levels remained elevated for several hours, gradually decreasing to preoperative levels the day after operation.

Other significant results include a rather remarkable immediate postoperative decrease in fibrinogen levels in nearly all (88 per cent) of the patients tested. The fibrinogen was very promptly replaced and very high levels were found the day after operation. This indeed may play a major role in postoperative thromboembolic sequellae.

These results show a definite relationship between the stress of operation and the hypercoagulable state. Excessively high IFA levels probably are a major factor in this potentially lethal state. On the other hand, high IFA levels can be prevented by the simultaneous administration of carbohydrates. Fibrinogen is used up at a rapid rate during the clotting processes associated with the trauma of operation, but is quickly replaced and indeed does apparently "rebound" postoperatively to significantly elevated levels.

- 40 -
***** ACKNOWLEDGMENTS *****

This work was inspired by Dr. Merle M. Musselman. His continued interest in its progress and his assistance in the preparation of this manuscript have been most gratifying.

I am indebted to Dr. Herbert L. Davis who offered invaluable criticism and information throughout all stages of this study. Further, I am obligated to Dr. and Mrs. Davis who spent many hours supervising and performing the countless numbers of laboratory tests involved in this project.

I wish also to thank Dr. Carl J. Potthoff for his assistance and guidance in the analysis of our accumulated data.

I thank Mrs. Mary Carder for her expert typing of this manuscript.

James B. Shields
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TABLE 2. RESULTS OF PATIENTS RECEIVING DEXTROSE

- 43 -
### TABLE 2. RESULTS OF PATIENTS RECEIVING DEXTROSE (Cont.)

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FIGURE 1. Lee-White Coagulation Times

Blue = patients receiving heparin
Red = patients not receiving dextrose

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Sample number 1

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FIGURE 3. Fibrinogen
FIGURE 5. Total Lipids

Legend:
- Blue = Patients receiving dextrose
- Red = Patients not receiving dextrose

Sample number 1

Sample number 18
FIGURE 6. Recalcified Clot Times (0.2 ml.)
FIGURE 7. Recalcified Clot Times (0.5 ml.)

Line = patients receiving lactose
Red = patients not receiving lactose
FIGURE 8. Procedure Time—Lee-White Clot Time (Immediate postoperative)

Blue = patients receiving dextrose

Red = patients not receiving dextrose
FIGURE 9. Procedure Time—Lee-White Clot Time (4 hour postoperative)

Blue = patients receiving dextrose
Red = patients not receiving dextrose

CLOT TIME IN MINUTES
1. Davis, H. L.: Davis Modification of the Trout Procedure for Serum Ionic Fatty Acid Determinations/ Personal communication to the author.

2. Davis Modification of the Fowell Procedure for Plasma Fibrinogen Determinations. Personal communication to the author.

3. Davis Modification of the Sigma Procedure for Serum Lipase Determinations. Personal communication to the author.


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